

Managing smoking cessation

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CMAJ Podcasts: author interview at <https://soundcloud.com/cmajpodcasts/151510-view>

Competing interests:

Robert Reid, Andrew Pipe, Debbie Aitken and Kerri-Anne Mullen are named developers of the Ottawa Model for Smoking Cessation, a registered trademark of the University of Ottawa Heart Institute, and have financial interest in the program. Andrew Pipe has received consultant and lecture fees from Johnson & Johnson and Pfizer Inc., consultant fees from GlaxoSmithKline and research funding from Pfizer Inc. Robert Reid has received lecture fees from Johnson & Johnson Inc. and Pfizer Inc., and has held a research grant through the Pfizer Global Research Awards for Nicotine Dependence competition. No other competing interests were declared.

This article has been peer reviewed.

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CMAJ 2016; DOI:10.1503/cmaj.151510

Most people who smoke in Canada (64.4%) report that they want to quit, and half (49.6%) have tried to quit in the past year.¹ Unfortunately, less than five percent of such attempts result in long-term abstinence.² Smokers experience pleasure, reduced stress and anxiety, and augmentation of certain physical and mental functions when nicotine inhaled in tobacco smoke attaches to brain receptors, triggering the release of dopamine and other neurotransmitters.³ Abstinence from smoking triggers symptoms of withdrawal from nicotine (e.g., irritability, depressed mood, restlessness, anxiety) and cravings to smoke. Smoking, although a response to nicotine addiction, is also a highly conditioned behaviour: specific moods, situations or settings are associated with the rewarding effects of nicotine and often trigger relapse.³

Health care providers can be instrumental in motivating attempts at smoking cessation and enhancing the success of these attempts.⁴ Although effective treatments exist for those who are motivated to quit, only 30%–35% of people who smoke indicate that they are ready to stop in the next 30 days.^{5,6} New research points to the effectiveness of interventions for smokers not motivated to quit but interested in reducing their smoking,⁷ as well as interventions to increase interest among the unmotivated.⁴ As a result, physicians now have the tools to offer assistance to most smokers encountered in practice.⁸

We review evidence-based pharmacotherapies and behavioural treatments for smoking cessation, describe how these treatments can be effectively combined for patients with varying treatment goals, illustrate practice- and provider-level supports that make it easier to manage smoking cessation and provide updates on smoking cessation in patients with mental illness, treatments for smokers who are or wish to become pregnant, and the use of electronic cigarettes (e-cigarettes) as cessation aids (Box 1).

What medications can help patients to quit smoking?

Three cessation medications are approved for use in Canada: nicotine replacement therapy, bupropion and varenicline.

Nicotine replacement therapy is available in different formulations and provides temporary replacement of the nicotine from cigarettes; the therapy is aimed at reducing motivation to smoke and symptoms of nicotine withdrawal.

The patch form of nicotine replacement slowly delivers nicotine over 16 or 24 hours. The gum, inhaler, lozenge and oral spray forms of nicotine replacement treatment deliver nicotine more rapidly, but the effects are short-lived. There are no absolute contraindications to this treatment; however, physician consultation has been advised when treating patients with cardiovascular disease and those patients who are pregnant. Given the benefits of cessation, such caveats should rarely prevent use of nicotine replacement therapy.^{9,10} A 2013 meta-analysis of treatment-specific reviews in the Cochrane Database reported an odds ratio (OR) of 1.84 (95% confidence interval [CI] 1.71–1.99) for nicotine replacement therapy versus placebo.¹¹

Bupropion is an atypical antidepressant and a weak inhibitor of the neuronal uptake of norepinephrine, serotonin and dopamine¹² that increases the odds of quitting versus placebo (OR 1.85, 95% CI 1.63–2.10); there are strict contraindications to its use in patients who are at increased risk of seizure.¹²

Varenicline, a nicotine receptor partial agonist/antagonist, maintains moderate levels of dopa-

KEY POINTS

- Smokers may be interested in quitting abruptly, reducing their smoking before quitting on a quit date, reducing their smoking but not in setting a quit date, or neither quitting nor reducing their smoking; the interventions used will vary according to treatment goal.
- The implementation of systematic approaches, such as the Ottawa Model for Smoking Cessation, can help physicians to identify patients who smoke and offer them evidence-based assistance.
- Interventions using a combination of pharmacotherapy and behavioural support are most effective.
- People with no immediate intention to quit smoking but who are interested in reducing the amount they smoke, can achieve long-term abstinence through a smoking-reduction intervention mediated by nicotine replacement therapy or varenicline.

mine, which reduces withdrawal symptoms and smoking satisfaction by preventing attachment of nicotine to certain nicotine receptors.¹³ Varenicline increases the odds of quitting smoking compared with placebo (OR 2.89, 95% CI 2.40–3.48).¹¹

Combining medications

Combination nicotine replacement therapy (i.e., pairing a nicotine patch with nicotine gum, lozenges, inhalers or oral sprays) is more effective than placebo (OR 2.73, 95% CI 2.07–3.65) or nicotine replacement monotherapy (OR 1.34, 95% CI 1.00–1.8).¹¹

Nicotine replacement therapy in conjunction with bupropion has a modest but significant effect (OR 1.24, 95% CI 1.06–1.45), with no increase in adverse events versus bupropion treatment alone.¹⁴

Varenicline in conjunction with a nicotine replacement patch is more efficacious than varenicline alone (OR 1.62, 95% CI 1.18–2.23),¹⁵ with no increase in adverse events. Combined treatment with varenicline and bupropion increases short-term but not long-term cessation rates versus treatment with varenicline alone.¹⁶

Medications for smoking reduction

Many people who smoke have made abrupt, unsuccessful attempts at quitting, and many are discouraged by this approach. Strategies to reduce and quit smoking identify a specific day to quit, as in abrupt cessation, but smokers reduce smoking before this date; pharmacotherapy starts in the pre-quit reduction period.¹⁷

A systematic review and meta-analysis of 10 randomized controlled trials (RCTs) involving 3760 participants concluded that interventions to reduce and quit smoking produced cessation rates comparable to quitting abruptly.¹⁸ There is also evidence that cessation medications and support can be offered to smokers with no immediate intention to quit, but who are interested in reducing their smoking.⁷ A 2015 systematic review and meta-analysis involving 7981 participants who smoked supported the efficacy of using nicotine replacement therapy or varenicline to achieve long-term cessation among patients who want to reduce their smoking.⁷ Participants were given standard doses of nicotine replacement therapy or varenicline for periods of 2–18 months. Cessation rates measured at least 6 months after starting treatment ranged from 4.2% to 17.5% for reduction support in conjunction with medication compared with a range of 2.6% to 12.2% with no intervention.⁷

Adverse effects of medications

A network meta-analysis of cardiovascular events associated with pharmacotherapies for

smoking cessation, which included data from 21 RCTs of nicotine replacement therapy, 28 of bupropion treatment and 18 of varenicline treatment, found no increase in the risk of cardiovascular events with bupropion (relative risk [RR] 0.98, 95% CI 0.54–1.73) or varenicline (RR 1.30, 95% CI 0.79–2.23),¹⁹ and an elevated risk associated with nicotine replacement therapy mostly because of less serious events such as palpitations (RR 2.29, 95% CI 1.39–3.82). A reduction in major adverse cardiovascular events was noted for treatment with bupropion (RR 0.45, 95% CI 0.21–0.85), and there was no clear evidence of harm with varenicline treatment (RR 1.34, 95% CI 0.66–2.66) or nicotine replacement therapy (RR 1.95, 95% CI 0.26–4.30).

A review of the neuropsychiatric safety of varenicline, including data from 22 industry- and 17 non-industry-funded RCTs that involved 10 761 participants, found no increased risk of suicide or attempted suicide, suicidal ideation, depression, irritability, aggression or death in participants taking varenicline compared with those taking placebo,²⁰ which is consistent with other reviews.^{21,22} An RCT mandated by the US Food and Drug Administration, which assessed the incidence of neuropsychiatric events among 8144 participants who smoke and were given treatment with varenicline, bupropion, nicotine replacement therapy patches or placebo, found no increased risk of neuropsychiatric events attributable to varenicline or bupropion relative to nicotine replacement therapy or placebo.²³ Data from surveillance studies involving patients using bupropion for smoking cessation showed an increased risk of seizures;^{24,25} safety could be improved if clinicians avoid treatment with bupropion in patients at risk of seizures, including older adults.

What behavioural treatments can help patients quit?

Adding behavioural treatments to pharmacotherapy increases cessation rates;^{17,26} both should be offered to patients. When treatments are combined, long-term abstinence rates approach 25%–30%.⁴

Box 1: Evidence used in this review

We searched PubMed, Cochrane and MEDLINE databases using combinations of the terms “tobacco-use cessation,” “smoking cessation,” “pharmacotherapy,” “medication,” “counseling,” “behavioural” and “review” along with the “related articles” function, and we restricted our search to research published since 2005. We focused attention on recently published research: in particular, systematic reviews, systematic reviews of reviews and randomized controlled trials. We selected interventions for smoking cessation that illustrated salient clinical issues for our review, with an emphasis on evidence relevant to the Canadian context.

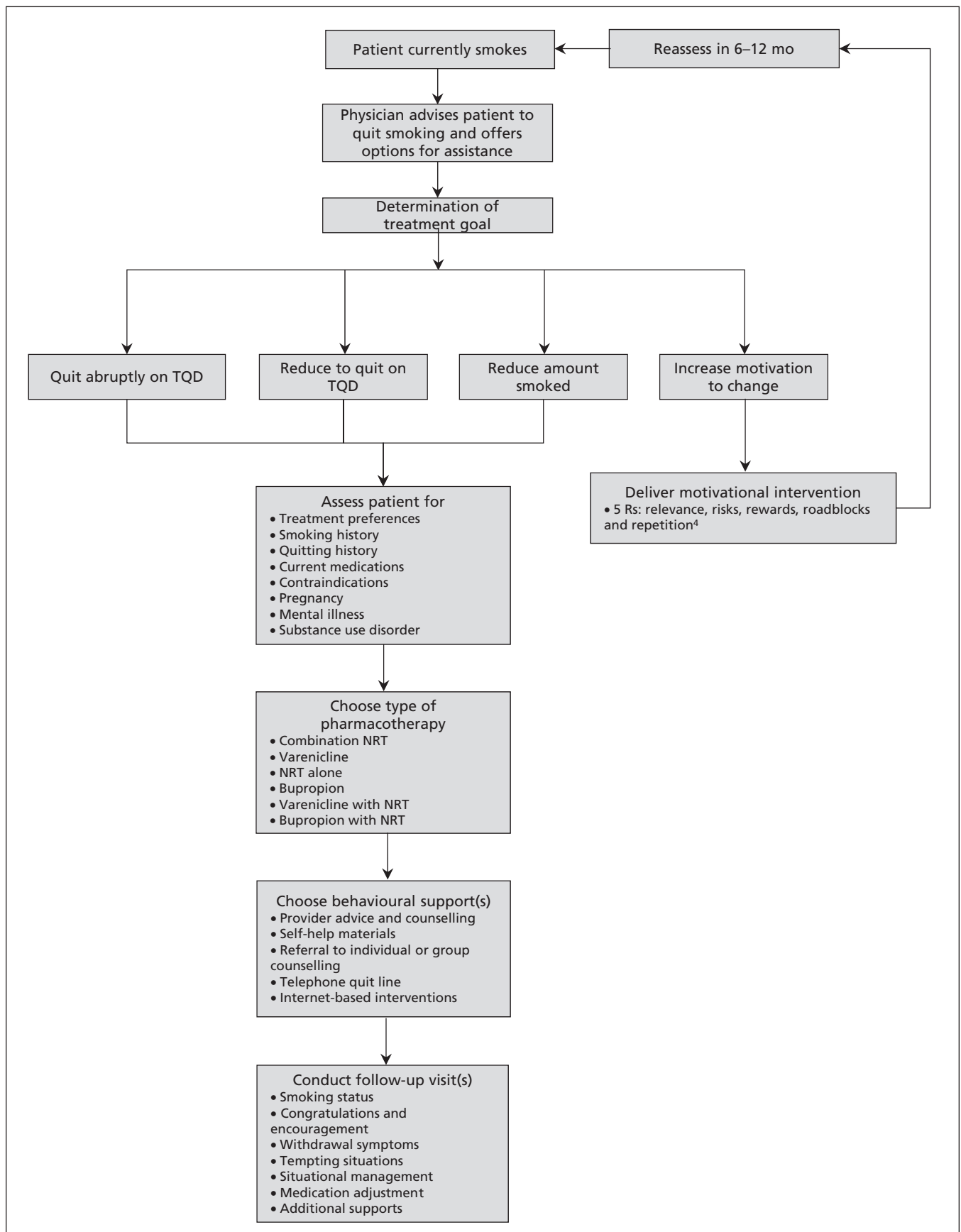


Figure 1: Flow chart to guide selection of treatments for smoking cessation (adapted from Hughes).¹⁰ Note: NRT = nicotine replacement therapy, TQD = target quit date.

Provider-delivered treatments

Brief advice can increase the likelihood of short-term abstinence by 30%.⁴ Intensive cessation advice and counselling has a higher likelihood of getting smokers to quit compared with brief advice (OR 1.37, 95% CI 1.20–1.56).²⁷ Two approaches to counselling yield significantly higher abstinence rates: practical counselling for problem-solving skills (e.g., dealing with other smokers, managing cravings, anticipating situations where temptation to smoke will be high [e.g., low mood, alcohol use]); and emotional support (e.g., expressing confidence in the patient's ability to quit, praising actions taken and successes).⁴ Tailored self-help materials can boost the effectiveness of provider-delivered treatments (OR 1.20, 95% CI 1.02–1.30).⁴

Adjunct behavioural treatments

Those motivated to quit smoking may be referred to individual or group counselling offered by community providers. Counselling typically focuses on problem-solving skills, relaxation training and coping techniques, and group counselling adds elements of peer support. Individual or group counselling increase abstinence rates relative to self-help (1.39 [95% CI 1.24–1.57]²⁸ and 1.98 [95% CI 1.60–2.46],²⁹ respectively.

All provinces and territories in Canada provide no-cost access to telephone quit lines. Despite evidence of their effectiveness, quit lines are used by less than 2% of smokers.¹ A 2013 review of studies of telephone counselling found positive effects for interventions involving multiple sessions of proactive counselling compared with self-help or single-session brief counselling (RR 1.41, 95% CI 1.20–1.66).³⁰

A review of studies involving Internet-based programs for smoking cessation found a significant effect at 6 months or longer follow-up compared with self-help materials or usual care (RR 1.48, 95% CI 1.11–2.78).³¹ Internet-based support for those looking to stop smoking in Canada is available at smokershelpline.ca.

What factors should be considered in choosing a treatment strategy?

It is important to establish practice routines that ensure a consistent systematic approach to treatment for tobacco use. One approach that has been widely disseminated in Canada (> 350 sites) is the Ottawa Model for Smoking Cessation — a proven process for integrating tobacco-dependence treatments within clinical settings.^{5,32–35}

The Ottawa Model for Smoking Cessation ensures providers receive training in treatment

for tobacco dependence, and introduces reminders (e.g., prompts by electronic medical records) and practice tools to ensure that all patients are asked about their smoking status, given unambiguous nonjudgmental advice to quit smoking, offered assistance in the form of pharmacotherapy and behavioural support, and offered ongoing follow-up (≥ 6 mo) (Figure 1). Implementation of the Ottawa Model for Smoking Cessation is associated with significant increases in long-term abstinence and improvements in health and utilization of health care among smokers in hospital settings (OR 1.71, 95% CI 1.11–2.64),^{34,36} and in primary care settings (adjusted OR 3.10, 95% CI, 1.10–8.60).^{6,33,34}

Box 2: Applying the results of this review in clinical practice (fictional case)

A 55-year-old woman who had recently undergone angioplasty for unstable angina presented to the physician's office. She had smoked 25 cigarettes per day for the past 37 years. She was willing to quit but wanted to reduce the amount she smoked before stopping completely. Her husband also smoked but was unwilling to quit at present. In addition to heart disease, she was being treated for anxiety with citalopram and lorazepam.

To facilitate smoking reduction, a target quit date of four weeks after the initial office visit was selected. She was prescribed a daily nicotine patch (21 mg) and advised to reduce the amount she was smoking by at least 50% over the next month. She received written instructions on how to use the medication and tips for cutting cigarette consumption. She was also prescribed a nicotine inhaler to use when she had a craving to smoke. Counselling focused on proper use of the medication, and she was advised to have her husband assist her by not smoking in the home and car.

At her next visit, one week before her quit date, the patient reported that she was smoking eight cigarettes per day. She asked to switch to varenicline, because she was eligible for coverage for that drug. Counselling focused on tactics using delay, avoidance and substitution to deal with cravings and tempting situations.

The patient began taking varenicline the day after her office visit and used the nicotine patch for an additional week. She continued to carry a nicotine inhaler for cravings and was referred to the quit line for additional counselling. At follow-up visits that occurred one week, and one and three months after her quit date, she reported that she was not smoking.

Table 1: Effectiveness of medications for smoking cessation relative to placebo (adapted from data provided in Cahill et al.¹¹)

Medication	No. of studies	Estimated OR (95% CI)
NRT patch	43	1.91 (1.71–2.14)
NRT gum	56	1.68 (1.51–1.88)
Other type of NRT (e.g., lozenge, inhaler, oral spray)	16	2.04 (1.75–2.38)
Combination NRT	2	2.73 (2.07–3.65)
Bupropion	36	1.85 (1.63–2.10)
Varenicline	15	2.89 (2.40–3.48)

Note: CI = confidence interval, NRT = nicotine replacement therapy, OR = odds ratio.

Goals of treatment

Although complete abstinence is the ultimate goal, only 30%–35% of smokers are ready to quit within the next 30 days at any given time.^{5,6} Smokers may have one of four potential goals for their smoking behaviour: they are interested in quitting abruptly on a target quit date, they are interested in reducing their smoking before quit-

ting on a target quit date, they are not interested in setting a target quit date but are interested in reducing their smoking, or they are not interested in quitting or reducing their smoking. Intervention should match the treatment goal, with the recognition that appropriate advice and encouragement can positively influence those who are undecided (Box 2).

Table 2 (part 1 of 2): Suggestions and timelines for provider-delivered advice and counselling for patients with varying treatment goals

Treatment goal	Suggested procedures and timelines	
	Precessation	Post-TQD follow-up visit(s)
Quit abruptly on TQD ⁴	<p>Initial visit</p> <ul style="list-style-type: none"> • Set TQD within next 4 wk • Provide written instructions for use of pharmacotherapy • Express confidence in patient's ability to succeed • Focus on problem-solving (e.g., anticipate difficult situations and discuss coping strategies) • Remind patient to book follow-up 1–2 wk after TQD • Refer patient to adjunct behavioural support (i.e., individual or group counselling, telephone quit line, Internet-based support) • Provide self-help material <p>Preparation visit (optional)</p> <ul style="list-style-type: none"> • Preparation visit recommended 1 wk before TQD • Ensure patient has begun pharmacotherapy • Reinforce advice and encouragement provided during the initial visit 	<ul style="list-style-type: none"> • Follow-up visits recommended at wk 1 and mo 1–3 after TQD • Assess smoking status • Congratulate those who have quit smoking • Query patient about adverse events • Encourage continued use of pharmacotherapy • Identify triggers and discuss coping strategies • If relapse has occurred, discuss reasons for relapse and treatment goal
Reduce to quit on TQD ^{38–41}	<p>Initial visit</p> <ul style="list-style-type: none"> • Set TQD within next 4 wk • Patient to begin using medication 2–4 wk before TQD • Provide written instructions for use of pharmacotherapy • Express confidence in patient's ability to succeed • Focus on problem-solving (e.g., anticipate difficult situations and discuss coping strategies) • Set reduction goals: decrease number of cigarettes per day by $\geq 25\%$ during first week, $\geq 50\%$ during second week and $\geq 75\%$ by TQD • Suggest two common reduction techniques: systematically increase the amount of time between cigarettes; or rank order cigarettes from easiest to hardest throughout the day, then systematically start to eliminate on each day, from easiest to hardest • Remind patient to book follow-up visit 1–2 wk after TQD • Refer patient to adjunct behavioural support (i.e., individual or group counselling, telephone quit line, Internet-based support) • Provide self-help material <p>Preparation visit (optional)</p> <ul style="list-style-type: none"> • Preparation visit recommended 1 wk before TQD • Ensure patient has begun using pharmacotherapy • Congratulate those who have reduced or quit smoking • Reinforce advice and encouragement provided during the initial visit • If patient has not reduced smoking, consider adjusting treatment 	<ul style="list-style-type: none"> • Follow-up visits recommended at wk 1 and mo 1–6 after TQD • Assess smoking status • Congratulate those who have quit smoking • Query patient about adverse events • Encourage continued use of pharmacotherapy • Identify triggers and discuss coping strategies • If relapse has occurred, discuss reasons for relapse and discuss treatment goal

Table 2 (part 2 of 2): Suggestions and timelines for provider-delivered advice and counselling for patients with varying treatment goals

Treatment goal	Suggested procedures and timelines	
	Precessation	Post-TQD follow-up visit(s)
Reduce smoking ^{42–47}	<ul style="list-style-type: none"> • Explain how pharmacotherapy can be used to help reduce amount smoked • Encourage patient to set reduction goal (e.g., by 50%) or to reduce as much as possible • Suggest 2 common reduction techniques: systematically increase the amount of time between cigarettes; or rank order cigarettes from easiest to hardest throughout the day, then systematically start to eliminate on each day, from easiest to hardest • Refer patient to adjunct behavioural support (i.e., individual or group counselling, telephone quit line, Internet-based support) • Provide self-help material 	<ul style="list-style-type: none"> • Schedule follow-up within first month after smoking reduction • Query patient about adverse events • Query patient about success with reduction • Encourage patient to set new reduction goal • Ask if patient is interested in quitting; if patient wants to quit, set TQD and begin or schedule a preparation visit • Remind patient to book a follow-up visit if they decide they want to quit
No intention of reducing or quitting ⁴	<ul style="list-style-type: none"> • Conduct motivational intervention with the patient using “the 5Rs.” Ask the patient to identify: 1) why smoking is personally relevant; 2) the potential risks of continued tobacco use; 3) the potential rewards (benefits) of quitting; and 4) the potential roadblocks to quitting. 5) Repeat motivational interventions every 6–12 months. • Remind patient to book a follow-up visit if they become interested in quitting • Refer patient to adjunct behavioural support (i.e., individual or group counselling, telephone quit line, Internet-based support) • Provide self-help material 	<ul style="list-style-type: none"> • Ask if patient is interested in quitting; if patient wants to quit, set TQD and begin or schedule a preparation visit • Conduct motivational intervention • Remind patient to book a follow-up visit if they decide they want to quit

Note: TQD = target quit date.

Unmotivated smokers

If patients are not motivated to quit or reduce their smoking, clinicians can enhance motivation during a brief conversation guided by recommendations in the 2008 update of the Clinical Practice Guideline from the Tobacco Use and Dependence Guideline Panel of the US Department of Health and Human Services (i.e., “the 5 Rs”: exploring personal “relevance” of quitting, potential “risks” of continued tobacco use, potential “rewards” of quitting, “roadblocks” to quitting and “repetition” of a motivational intervention at every visit to the clinic setting (suggested follow-up every 6–12 mo).⁴ Interest in quitting or reducing smoking can be reassessed following this discussion. Tobacco users who have failed in previous cessation attempts can be reminded that most people make repeated attempts to quit before achieving success.

How to assess patients willing to change their smoking behaviour

Important patient-related factors to be assessed include treatment preference, history of smoking, quitting history, current medications, contraindications, pregnancy, and the presence of mental

illness and/or other substance-use disorders. Many smokers have made previous cessation attempts; these efforts are important sources of information. Use of cessation medications, adherence and reasons for relapse are particularly informative in developing a treatment strategy. Those who smoke ≥ 25 cigarettes per day and/or have their first cigarette less than 30 minutes after waking, and those with mental illness or substance-use disorders may require higher doses and longer durations of cessation medication, with more frequent follow-ups.²⁶

Choosing between pharmacotherapy options

Pharmacotherapy will be required in almost all instances in which patients wish to quit completely or to reduce the amount they smoke to maximize chances of success (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.151510/-/DC1). Medication choice is driven by several considerations, including patient preference and past experience, contraindications, cost (and coverage for medications) and efficacy. Combination nicotine replacement therapy or varenicline are the most effica-

cious pharmacotherapy treatments¹¹ (Table 1). People who are profoundly addicted to tobacco may benefit from high-dosage (> 22 mg/d) nicotine replacement therapy delivered via the patch.³⁷

Choosing behavioural support options

Clinician advice and assistance (Table 2) are the mainstays of behavioural support; however, they can be supplemented with self-help materials and referrals to individual and group-based counselling programs, telephone quit lines and Internet-based interventions. There is a positive relation between ongoing person-to-person contact and successful outcomes;⁴ therefore, smokers should engage in as much behavioural support as is feasible.¹⁰

Follow-up

Because addiction to tobacco is a chronic relapsing condition, follow-up is critical to treatment. The timing and frequency of follow-up is dependent on the treatment goal (Table 2). For patients who are achieving their treatment goal (i.e., smoking cessation or reduction), congratulate and consider if adjustments to treatment are appropriate. If treatment goals are not being met, it is important to identify the cause(s) (e.g., high levels of craving and withdrawal symptoms, poor treatment compliance, stressful situations, presence of other smokers or alcohol use) and assess if there is a need for augmentation or alteration of the treatment approach — including medication titration.

Treating smokers with mental illness

Rates of cigarette smoking are two to four times higher in people with current mood, anxiety and psychotic disorders.⁴⁸ A 2015 review of studies assessing smoking cessation treatment in patients with schizophrenia, depression, anxiety disorders and posttraumatic stress disorder showed that smokers with chronic mental illness can quit smoking using standard cessation approaches, without adverse effects on psychiatric symptoms.⁴⁹ Two RCTs^{50,51} evaluating

varenicline for smoking cessation and a systematic review⁵² showed that bupropion and varenicline are effective in patients with schizophrenia. Two RCTs^{53,54} and a systematic review and meta-analysis⁵⁵ found that varenicline was effective in patients with depression and severe mental illness. Fewer studies have reported about treatments for smoking cessation in patients with anxiety disorders and posttraumatic stress disorder; therefore, appropriately powered RCTs involving these populations are needed.⁴⁹ Relapse rates are higher in those with mental illness, which suggests that additional support and prolonged treatment are needed.

How to manage pregnant women who smoke

The Canadian Smoking Cessation Clinical Practice Guideline (from the Centre for Addiction and Mental Health)⁵⁶ and the Society of Obstetricians and Gynaecologists of Canada⁵⁷ recommend that counselling for smoking cessation should be considered as first-line intervention for smokers who are pregnant. If counselling is not successful, nicotine replacement therapy or bupropion may be considered after an informed discussion of the benefits and risks of treatment.^{56–58} Metabolism of nicotine is increased during pregnancy, which suggests that higher doses for nicotine replacement treatment may be required.⁵⁹

Can e-cigarettes help people to quit smoking?

E-cigarettes containing nicotine have been shown to help patients stop smoking over the long term compared with placebo (i.e., e-cigarettes that do not contain nicotine) in a few randomized trials.⁶⁰ A pragmatic RCT in New Zealand involving adult smokers who wanted to quit found that e-cigarettes containing nicotine showed similar cessation rates compared to nicotine patches.⁶¹ However, the small number of RCTs, low event rates and wide confidence intervals for the estimates suggest low certainty in results to date. A systematic review and meta-analysis that pooled results from 18 observational studies and two clinical trials found the odds of quitting smoking were 28% lower in those using e-cigarettes compared with nonusers.⁶²

Conclusion

Tobacco use is Canada's leading cause of preventable disease, disability and death. If smoking cessation occurs before the age of 40, 90% of premature morbidity and death will be eliminated

Box 3: Unanswered questions

- Many cigarette smokers are also regular marijuana users. "Co-smoking" may interfere with attempts to quit tobacco use. Marijuana smoking also increases breath carbon monoxide, which complicates biochemical assessment of tobacco use.
- Most smokers still attempt to quit without involving health care professionals. New ways to engage these smokers in evidence-based treatment are required.
- New approaches are required to reach younger smokers.

in these patients.⁶³ Gaps in our understanding are outlined in Box 3.

Clinicians can enhance the likelihood of successful smoking cessation by employing systematic approaches to the identification and treatment of smokers; pharmacotherapies and behavioural interventions are the mainstays of this treatment.

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Contributors: Robert Reid drafted the article. Gillian Pritchard, Kathryn Walker, Debbie Aitken, Kerri-Anne Mullen and Andrew Pipe revised it critically for important intellectual content. All of the authors contributed substantially to the conception and design of the article, and acquisition, analysis and interpretation of the data; gave final approval of the version to be published and agreed to act as guarantors of the work.